## REMARKS

The Office Action mailed May 25, 2010, was reviewed and the comments of the Patent and Trademark Office were considered. As of the last amendment, Claims 1 and 3-34 are pending and claims 8, 27 and 30-34 were withdrawn from consideration. By this response, Claims 1, 4, 6-8, 10 and 12-18 are amended and claim 2 is cancelled. New claims 35-36 are added. Support for the amendment can be found in the original claims and the specification, including for example, the publication at [0150]. Applicants further submit an English translation of the priority document FR 03 50887.

## CLAIMS OBJECTIONS

Claim 6 and 7 are objected for minor informalities. Applicant has amended claims 6 and 7 in order to correct these informalities.

## 35 USC § 112 REJECTIONS

Claims 1-7, 9-26, 28 and 29 are rejected under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The examiner alleges that claim 1 is unclear because it recites a limitation "wherein said formulation is a least partly caused by at least one physiological protein present *in vivo*". The applicant amended this claim in order to make it clearer.

It recites now

1. (Currently Amended) A liquid pharmaceutical formulation for the prolonged release of active principle(s) (AP), said formulation comprising an aqueous colloidal suspension of low viscosity based on submicronic particles of water-soluble biodegradable polymer [PO] carrying hydrophobic groups [HG] said submicronic particles being non-covalently associated with at least one active principle (AP), wherein:

the dispersion medium of the suspension comprises water;

the concentration of [PO] is such that [PO] ≥ 0.9.C1, where C1 is the "*induced gelling*" concentration of the particles of PO, as measured in an IG test,

making it possible to prolong and control the *in vivo* release time of the AP beyond 24 h after administration;

said formulation is liquid under the injection conditions;

and said formulation is liquid at the physiological temperature and at the physiological pH and in the presence of:

a physiological electrolyte in a physiological concentration,

or at least one surfactant.

Claim 2 has been canceled.

Claim 7 has been amended to define the range for the variables "n" and "m".

Claim 8 has been amended and n' has been replaced by n", as stated in the application as published at paragraph [0150].

The examiner alleges that claims 17-20 recite a limitation that has insufficient antecedent basis. Claim 17 and 18 have been amended and "*the* polyalkylene glycol type" has been replaced by "polyalkylene glycol type", thus creating an antecedent basis for the claims depending from claim 17.

The applicant respectfully requests the Examiner withdraws the rejection of these claims as being indefinite under 35 U.S.C. § 112, second paragraph.

## CLAIM REJECTIONS - 35 USC § 102

**Claims 1-3, 6, 16, 21-23, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Huille *et al.* (US 6,630,171).**

The main objective of the current invention is to find a formulation allowing an increased prolonged release time of the active ingredient, such that this release time is beyond 24h after administration *in vivo*. The applicant discovered that such objective could be met using a suspension of a polymer PO, bearing hydrophobic groups attached laterally to the chain that must have a concentration of polymer PO greater than a critical concentration of 0.9 C1 corresponding to the formation of a gel in presence of BSA in an IG test (See specification at

page 5, [0100] and followings). As such, the claims require "[PO] ≥ 0.9.C1, where C1 is the "*induced gelling*" concentration of the particles of PO, as measured in an IG test."

Huille does neither mention nor suggest a critical concentration of polymer of greater or equal to 0.9 C1. Further, Huille neither mentions nor suggests the existence of a critical concentration above which the release time of the active ingredient is beyond 24 h after administration. Thus the key of the current invention is that the pharmaceutical composition must fulfill a non obvious restrictive condition, namely that the concentration of polymer PO should be greater than a critical concentration of 0.9 C1. Therefore, Huille cannot anticipate the current claims.

This is also to the applicant's credit to have developed and fine-tuned an IG test that allows determining the value of the above mentioned concentration C1. More precisely, C1 is the concentration at which the formulation forms a gel *in vitro* without requiring a temperature or pH change, in presence of a specified concentration of BSA, namely 30mg/ml (See specification at page 5, [0102]).

This critical concentration 0.9 C1 at which the release time is significantly increased is now defined in amended first claim. The relation between this concentration 0.9 C1 and the *in vitro* protein-induced gelling phenomenon is novel. These observations were not disclosed in the prior art Huille and have been discovered by the Applicant.

Thus amended independent claim 1 is not anticipated by Huille. Therefore, claims 2, 3, 6, 16, 21-23, 25 and 26 depending from amended claim 1 are also not anticipated. For these reasons, the Applicant respectfully request these rejections be withdrawn.

**Claims 1 to 3 are also rejected under 35 U.S.C. 102(e) as being anticipated by Lambert (US 7,030,155).**

Lambert does not anticipate the claims because Lambert does not teach the limitations of "submicronic particles of water-soluble biodegradable polymer [PO] carrying hydrophobic groups [HG]" and "[PO] ≥ 0.9.C1, where C1 is the "*induced gelling*" concentration of the particles of PO, as measured in an IG test" as required by the claims.

Lambert teaches that a custom surfactant can be "a vitamin E derivative comprising a peptide bonded polyglutamate attached to the ring hydroxyl and pegylated phytosterol." Lambert at col. 8, ll. 29-31. Lambert, therefore, teaches and discloses a surfactant including

alpha-tocopherol bonded to a polyglutamate and pegylated phytosterol. The examiner alleges that the tocopherol disclosed in Lambert is equivalent to the hydrophobic group of the instant invention, the polyglutamate to the [PO] and phytosterol to the AP.

One of skill in the art would understand that the peptide disclosed in Lambert is a chain-end linking polyglutamate binding to alpha-tocopherol. For example in col 6, ll 61-67 and in Scheme II, one molecule of PEG is bonded to one alpha-tocopherol via one succinic acid diester. Lambert therefore, teaches and discloses a polyglutamate that has only one alpha-tocopherol residue per molecule of polyglutamate. Amended Claim 1 of the instant application requires polymer [PO] which can carry several hydrophobic groups [HG]. Furthermore, these hydrophobic groups are grafted on the side chains of the polymer [PO] and not only at the chain-end. Lambert, by contrast, teaches a linear conjugate of vitamin E derivative. Thus, the composition of Lambert is different from the composition of Claim 1 of the instant application. One of skill in the art would appreciate that a polyglutamate bearing a multiplicity of hydrophobic groups on their side chains would have different structure and properties from a polyglutamate bonded to only one alpha-tocopherol.

Moreover, to obtain a release time of the active ingredient beyond 24 h after administration Claim 1 requires a critical concentration of 0.9 C1 in an IG test. Lambert does not anticipate the existence of a critical concentration for which the release time is greatly increased. Additionally this document does not disclose how to perform such a test in order to determine the 0.9 C1 critical concentration. The critical concentration 0.9 C1 at which the release time is significantly increased, as well as the relation between this concentration 0.9 C1 and the *in vitro* protein-induced gelling phenomenon, are totally new.

The Applicant, therefore, respectfully submits that Lambert does not anticipate amended Claim 1 and respectfully request the Examiner withdraw the rejection of Claim 1 under 35 U.S.C. § 102(e).

## CLAIM REJECTIONS - 35 USC § 103

Claims 1-3, 6, 7, 12-16, 21-26, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan (US 2006/0099264 A1), now issued as US 7,683,024.

The Applicant believes that this rejection is improper because Chan does not qualify as prior art under 102(e). Under § 102(e)(2), Chan is available as 102(e)(2) art as of the earlier of (i) the date the 371(c)(1), (2) and (4) requirements were satisfied or (ii) the international filing, as long as the application designated the US and international application was published in English.

Chan was filed as a US national stage application of WO 03/10403, which designated the US, and published June 3, 2003. However, this publication was in the French language with **only** an English Abstract. As such, the international application **was not published in English.** Thus, the prior art date of Chan is not the international application filing date. Instead, the applicable date for Chan would be the date the 371(c)(1), (2) and (4) requirements were satisfied, i.e. October 3, 2005. October 3, 2005 is after the priority date of this application. Thus, Chan does not qualify as prior art under 35 USC 102(e) and the rejection under 103(a) over Chan is improper.

## DOUBLE PATENTING REJECTION

Claims 1-7, 12-16, 21-23, 28 and 29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over co-pending Flamel applications (U.S. App. No. 10/580,037, U.S. App. No. 10/580,035). The rejection is improper because the cited references have the same priority date than the instant application, and thus cannot anticipate nor render obvious the amended claims.

The instant application claims priority to FR 03/50887, and thus has a priority date of November 21, 2003. The applications cited in the double patenting rejection have the exact same priority date as the instant application. For instance, U.S. App. No. 10/580,037 and U.S. App. No. 10/580,035 have a priority date of November 21, 2003. As such, Applicants respectfully request the rejection be withdrawn.

Claims 1-3, 6, 7, 12-16, 21-26, 28 and 29 are also rejected over claims 1-9 and 15-22 of the co-pending Chan (US Application No. 7,683,024). As noted in the above comments, Chan is not available as prior art under 102. Thus, Chan can neither anticipate nor render the amended claims obvious. Furthermore, Applicants note that the broadest claim in U.S. App. No. 7,683,024, claim 1, does not require submicronic particles of water-soluble biodegradable polymer (PO) carrying hydrophobic groups (HG) wherein the concentration of [PO] is such that

[PO] ≥ 0.9.C1, where C1 is the "*induced gelling*" concentration of the particles of PO, as measured in an IG test. These are all limitations required by the broadest instant claims. As such, the current claims patentably distinct from U.S. App. No. 7,683,024 and are not obvious. As such, Applicants respectfully request the rejection be withdrawn.

## CONCLUSION

In view of the above remarks and amendments, the Applicants respectfully submit that each of the pending objections and rejections has been addressed and overcome, placing all of the claims of the present application in condition for allowance. If the Examiner believes that personal communication will expedite prosecution of this application, or should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number provided below.

Applicants believe no fee is due with this submission. If a fee is due, however, the Direction is authorized to charge any additional fees that may be required in conjunction with this submission to Deposit Account Number 50-2228, under Order No. 022290.0159PTUS.

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Respectfully submitted,

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